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## Early View

Original article

### **Mechanisms of Orthopnoea in Patients with Advanced COPD**

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## **Mechanisms of Orthopnoea in Patients with Advanced COPD**

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## ABSTRACT

Many patients with severe chronic obstructive pulmonary disease (COPD) report unpleasant respiratory sensation at rest, further amplified by adoption of supine position (orthopnoea). The mechanisms of this acute symptomatic deterioration are poorly understood.

16 patients with advanced COPD and history of orthopnoea and 16 age- and sex-matched healthy controls (CTRL) underwent pulmonary function tests and detailed sensory-mechanical measurements including inspiratory neural drive (IND, diaphragm electromyography), oesophageal and gastric pressures in sitting and supine positions.

Patients had severe airflow obstruction ( $FEV_1$ :  $40 \pm 18$  %predicted) and lung hyperinflation. Regardless of the position, patients had lower inspiratory capacity (IC) and higher IND for a given tidal volume (i.e. greater neuromechanical dissociation (NMD)), higher intensity of breathing discomfort, minute ventilation ( $\dot{V}_E$ ) and breathing frequency ( $F_b$ ) compared with CTRL (all  $p < 0.05$ ). In supine position in CTRL (vs. sitting erect): IC increased (by 0.48L) with a small drop in  $\dot{V}_E$  mainly due to reduced  $F_b$  (all  $p < 0.05$ ). By contrast, patients' IC remained unaltered, but dynamic lung compliance decreased ( $p < 0.05$ ) in the supine position. Breathing discomfort, inspiratory work of breathing, inspiratory effort, IND, NMD and neuro-ventilatory uncoupling all increased in COPD in the supine position ( $p < 0.05$ ), but not in CTRL. Orthopnoea was associated with acute changes in IND ( $r = 0.65$ ,  $p = 0.01$ ), neuro-ventilatory uncoupling ( $r = 0.76$ ,  $p = 0.001$ ) and NMD ( $r = 0.73$ ,  $p = 0.002$ ).

In COPD, onset of orthopnoea coincided with an abrupt increase in elastic loading of the inspiratory muscles in recumbency in association with increased IND and greater neuromechanical dissociation of the respiratory system.

**Key words:** COPD, orthopnoea, dyspnoea, respiratory mechanics, inspiratory neural drive

### **Take Home Message**

Orthopnoea, a troublesome symptom in patients with severe COPD, is associated with increased neural drive to the diaphragm and heightened respiratory effort to compensate for abrupt augmentation of load-capacity imbalance of the inspiratory muscles.

### **Plain Language Summary**

Breathing discomfort is a common symptom in patients with severe chronic obstructive pulmonary disease (COPD) that further worsens in the recumbent position. This study advanced our understanding of reasons why such patients develop sudden breathing difficulty when lying flat. We discovered that increased breathlessness on lying down was linked to an abrupt increase in the drive to breathe from “control” centers in the brain, on account of the muscles of breathing being suddenly placed at a distinct disadvantage.

## INTRODUCTION

Dyspnoea is the most common respiratory symptom in patients with chronic obstructive pulmonary disease (COPD) and can be distressing even at rest, in those with severe airflow obstruction (1). In such patients, breathing discomfort can become further amplified on adoption of the supine position, i.e., orthopnoea (2-4). Indeed, in many individuals, orthopnoea may be problematic at night and disrupt sleep. The precise mechanisms of orthopnoea are unknown and their investigation presents a new opportunity to advance our understanding of the neurophysiology of dyspnoea.

Proposed factors contributing to orthopnoea include impedance of diaphragmatic motion in the supine position which may result in further mechanical disadvantage requiring compensatory increases in ribcage and accessory muscle activity to maintain ventilation (2,5). Heijdra *et al.* (5) have shown lower maximal inspiratory and expiratory mouth pressures in supine versus sitting in patients with severe COPD reflecting increased functional weakness of various respiratory muscles in recumbency. Increased airway resistance in the supine position, due to lower end-expiratory lung volume (EELV), is potentially important, although it is unclear whether this is relevant in patients with severe lung hyperinflation (3,6-8). Additionally, in some patients, worsening pulmonary gas exchange abnormalities due to gravitational effects and cephaloid shift of abdominal contents, could potentially stimulate chemoreceptors to increase inspiratory neural drive (IND) further compounding respiratory discomfort (9,10).

Important studies have shown that certain positions adopted by individual patients to relieve dyspnoea (e.g., “*forward-leaning*”) are associated with improved ability to generate maximal inspiratory pressures and improved length-tension relationships, neuromechanical efficiency of the diaphragm and reduced neuromechanical dissociation (NMD) of the respiratory system (2,4,11). This raises the question whether the opposite is true, i.e., that orthopnoea

reflects acute increases in inspiratory muscle dysfunction and reduced diaphragmatic efficiency. Collectively, most studies undertaken to-date lack validated measurements of dyspnoea intensity and included participants with heterogeneous physiological abnormalities and have not, therefore, permitted any definitive or unitary conclusions about the origins of orthopnoea in COPD.

Current constructs of the origins of dyspnoea in chronic lung diseases emphasize the importance of increased IND from cortical motor centres in the brain, secondary to load-capacity imbalance of the respiratory muscles (12,13). Advanced COPD showed higher IND (estimated by diaphragm electromyography (EMGdi)) at rest compared to healthy controls (14). Recent studies in which exercise was used as the provocative stimulus for dyspnoea, have shown that increased exertional dyspnoea intensity ratings are strongly associated with increased IND and increased disparity between IND and the mechanical response of the respiratory system (i.e. NMD) (15-19). Moreover, interventions that reduced mechanical loading of the inspiratory muscles (e.g. bronchodilators) or that improved their strength (e.g. inspiratory muscle training) are associated with reduced IND, and dyspnoea intensity in COPD (20,21). Accordingly, we postulated that orthopnoea is related to acute amplification of IND and NMD due to sudden deterioration in load-capacity ratio of already compromised inspiratory muscles in supine position. To test this hypothesis, we measured changes in dyspnoea intensity, IND, NMD, dynamic lung mechanics and pulmonary gas exchange during the transition from seated to supine positions in patients with advanced COPD with known orthopnoea and in healthy controls (CTRL).

## **METHODS**

### **Subjects**

We included sixteen patients with COPD: age  $\geq 45$  years; post-bronchodilator forced expiratory

volume in one-second  $<80$  %predicted; a cigarette smoking history  $\geq 20$  pack-years; clinically stable but with long-standing orthopnoea. Exclusion criteria: body mass index (BMI)  $>35$  kg/m<sup>2</sup>; use of oxygen; history of asthma or other respiratory/cardiovascular disease that could contribute to dyspnoea or orthopnoea (e.g. heart failure). Sixteen non-smoking age-matched CTRL were also included. Participants were recruited from a database of volunteers at the Respiratory Investigation Unit and respiratory outpatient clinics at Kingston Health Sciences Centre (Kingston, ON, Canada).

### **Study design**

This cross-sectional prospective study received ethical approval from the Queen's University and Affiliated Teaching Hospitals Research Ethics Board (DMED-1989-16). After providing informed consent, participants completed one visit, which included eligibility screening, symptom and quality of life (QoL) questionnaires (22-25), and pulmonary function tests (PFTs). We continuously measured EMGdi and respiratory pressures at rest while sitting erect then, after 10 minutes, in supine position using a double-ballooned multi-electrode oesophageal catheter. In each position, participants performed a series of cough, sniff and inspiratory capacity (IC) manoeuvres. Participants spent at least 5-minutes of quiet breathing while on a mouth piece to collect breath-by-breath breathing pattern and metabolic parameters.

### **Procedures**

Spirometry, plethysmography, lung diffusing capacity for carbon monoxide ( $D_LCO$ ), maximal inspiratory (MIP) and expiratory (MEP) mouth pressures were performed (Vmax229d, AutoboxV62J; SensorMedics, Yorba Linda, CA). Questionnaires included: modified Medical Research Council (MRC) dyspnoea scale (23), baseline dyspnoea index (BDI) (22), COPD assessment test (CAT) (25), and St. George Respiratory Questionnaire (24). Breath-by-breath breathing pattern and metabolic parameters (SensorMedics-Vmax229d), oxygen saturation by



pulse oximetry (SpO<sub>2</sub>) and heart rate (12-leads electrocardiogram) were collected.

At the end of quiet breathing period, participants were asked, using the modified 10-point Borg scale (26) to rate their intensity of breathing discomfort (*how strong?*): [0 indicating no discomfort, 10 maximal discomfort they ever experienced or could imagine experiencing] and quality of breathing discomfort (*what breathing feels like?*) in 5 domains: overall intensity, difficulty breathing in, difficulty breathing out, increased work/effort and unpleasantness (27).

*EMGdi and respiratory pressures:* data represent 30 participants as one in each group declined catheter insertion after initial agreement. A multi-electrode EMGdi catheter with oesophageal and gastric balloons was inserted nasally (16). EMGdi and respiratory pressures were continuously recorded and analysed (14,16,28). Raw EMGdi signal was sampled at 2,000 Hz (PowerLab-model-ML880; ADInstruments, Bella Vista, Australia), band-pass filtered between 20 and 1,000 Hz (Bioamplifier model-RA-8; Guanzhou Yinghui Medical Equipment Co., Guangzhou, China), and converted to a root mean square (RMS). For each breath, data from the electrode pair (from the five pairs) with the largest inspiratory RMS value were used for analysis. EMGdi,max was determined during maximal sniff or IC manoeuvres. The oesophageal and gastric balloons were connected to differential pressure transducers to obtain oesophageal (Pes) and gastric pressures (Pga). Trans-diaphragmatic pressure (Pdi) was calculated as the difference between Pes and Pga. Pdi,max and Pes,max were determined during maximal sniff manoeuvres (29). Tidal EMGdi as a percentage of EMGdi,max (EMGdi%<sub>max</sub>) and tidal Pdi as a percentage of Pdi,max (Pdi%<sub>max</sub>) were used as indices of the IND to the crural diaphragm and inspiratory effort, respectively (14,16,28). Ratios of EMGdi%<sub>max</sub> to tidal volume (V<sub>T</sub>)/predicted vital capacity (VC), EMGdi%<sub>max</sub>:tidal Pdi%<sub>max</sub> and EMGdi%<sub>max</sub>:minute ventilation ( $\dot{V}_E$ ) were used as indices of NMD, neuromuscular efficiency of the diaphragm, and neuro-ventilatory coupling, respectively. Expiratory flow limitation (EFL) was assessed as the % of V<sub>T</sub> that

overlapped the maximal flow volume loop of each position ( $V_{FL}$ ) (30). The PowerLab system received continuous flow signal input from the Vmax229d system for analysis. Airway resistance, dynamic lung compliance ( $CL_{dyn}$ ) and work of breathing (WOB) were calculated as previously described (16). More details are provided in the *online-supplement*.

### **Statistics:**

A sample size of 16 was estimated to provide 80% power to detect a 1 Borg-unit difference in dyspnoea intensity between-groups, based on a SD of one unit,  $\alpha$  of 0.05, and a two-tailed test of significance. Unpaired *t*-test was used for between-group comparisons and paired *t*-test to compare responses in sitting versus supine positions within groups. Linear regression was used to test the relationship between supine-sitting change in dyspnoea intensity and relevant independent variables in patients. Statistical significance was set at  $p < 0.05$ .

### **Results**

#### ***Subjects characteristics and PFTs***

Thirty COPD patients were screened: 14 were excluded (either because they didn't report long-standing orthopnoea and/or declined catheter insertion). Subjects' characteristics (**Table 1**, *online-supplement*): groups were matched for age, sex, height, and BMI. Three CTRL (with normal PFTs) had an insignificant smoking history and had stopped smoking for >30 years at the time of the study. Patients had greater activity-related dyspnoea (MRC dyspnoea scale and BDI), higher CAT scores, and poorer QoL compared with CTRL (all  $p < 0.001$ ). None of the participants had any clinical evidence of significant cardiac or pulmonary vascular disease that could contribute to orthopnoea. Other comorbidities and medications are shown in the *online-supplement*.

Compared to CTRL, patients had higher residual volume/total lung capacity (TLC) and

lower  $D_LCO$ , resting sitting IC, maximal voluntary ventilation, MIP and MEP (all  $p<0.01$ ), **table 1**. The ratio of alveolar volume measured by single-breath gas dilution to plethysmographic-TLC was lower in patients compared with CTRL ( $p<0.0001$ ) while TLC was not different between groups.

### ***Impact of COPD on dyspnoea, IND and ventilatory mechanics***

**Tables 2 and 3** summarize measurements in the supine and sitting positions. Patients had greater dyspnoea in all 5 domains in both positions compared with CTRL (all  $p<0.05$ ), **table 2**. In COPD patients, compared with CTRL, and regardless of body position,  $\dot{V}_E$  and ventilatory inefficiency (ventilatory equivalent for carbon dioxide ( $\dot{V}_E/\dot{V}CO_2$ )) were consistently higher; in the presence of lung hyperinflation (higher EELV, lower IC and inspiratory reserve volume (IRV)) and greater EFL ( $V_{FL}$ ) (all  $p<0.01$ ).  $V_T$  and  $PetCO_2$  were not different from CTRL in both positions (**figure 1, table 2**).  $P_{di,max}$  and  $P_{es,max}$  were lower (more negative) and airway resistance, total WOB, tidal EMGdi, IND, inspiratory effort and neuro-ventilatory uncoupling, were all greater in COPD vs. CTRL in both positions, all  $p<0.05$  (**table 3**).

### ***Impact of supine posture on dyspnoea, IND and ventilatory mechanics***

Dyspnoea ratings increased significantly in the transition from seated to supine position in COPD patients ( $p<0.05$ ), while CTRL reported no breathlessness (**table 2, online-supplement**). In supine (vs. sitting), CTRL's IC increased by 0.48L ( $p<0.001$ ) (**figure 1, online-supplement**) likely reflecting lower EELV; this was associated with lower  $\dot{V}_E$ ,  $\dot{V}_E/\dot{V}CO_2$ ,  $\dot{V}_E/\dot{V}O_2$ , and breathing frequency ( $Fb$ ) (all  $p<0.05$ ) with no change in  $V_T$  (**figure 1, table 2**). In contrast to CTRL, patients' IC, EELV,  $\dot{V}_E$ , and  $Fb$  did not change in the supine position (**table 2, figure 1**).  $V_T$  also remained unchanged. In supine vs. sitting, patients had lower  $\dot{V}_E/\dot{V}O_2$  and  $\dot{V}_E/\dot{V}CO_2$

( $p=0.001$ ) reflecting a slightly lower  $\dot{V}_E$  ( $p=0.07$ ) while  $\dot{V}O_2$  and  $\dot{V}CO_2$  remained unchanged. End-tidal  $CO_2$  ( $P_{et}CO_2$ ) did not change with position in CTRL, but slightly increased by 1.2 mmHg in supine vs. sitting position in COPD patients ( $p=0.003$ ). There was a minor drop in  $SpO_2$  in supine vs. sitting by 1% in CTRL ( $p=0.003$ ) and by 0.7% in patients ( $p=0.02$ ) (**table 2**).

In CTRL, supine positioning was associated with a small reduction in  $P_{es,max}$  ( $p=0.01$ ),  $P_{di,max}$  ( $p<0.01$ ) and  $EMG_{di,max}$  ( $p=0.004$ ), **table 3, online-supplement**. There were no differences in tidal  $EMG_{di}$ , IND, airway resistance, WOB, inspiratory effort, NMD, neuromuscular efficiency of the diaphragm or neuro-ventilatory coupling, but  $CL_{dyn}$  was lower ( $p=0.04$ ) and  $V_{FL}$  was higher ( $p=0.001$ ) in supine vs. sitting (**table 3, figure 2**). Expiratory muscle activity was reduced while supine [lower tidal expiratory  $P_{ga,max}$  ( $p=0.004$ ) and end-expiratory  $P_{ga}$  ( $p=0.047$ ) in supine vs. sitting], **table 3**.

Similar to CTRL, supine posture in COPD patients was associated with reductions in  $EMG_{di,max}$ ,  $P_{di,max}$ ,  $CL_{dyn}$  and expiratory muscle activity (all  $p<0.05$ ) with no change in airway resistance, **table 3, online-supplement**. Absolute tidal  $EMG_{di}$  was not different on average but has risen in 53% of patients while supine, **table 3, online-supplement**. Moreover, in patients with COPD, supine posture was associated with greater IND, NMD, neuro-ventilatory uncoupling and total inspiratory WOB (all  $p<0.05$ ), but neuromuscular efficiency of the diaphragm was unaltered, **table 3, figure 2**. Elastic WOB was also greater in supine vs. sitting ( $p=0.06$ ), **table 3**. Unlike CTRL, patients had greater inspiratory effort and ratio of  $P_{di,max}:V_{T\%VC}$  in supine vs. sitting position (**table 3, figure 2**). A descriptive summary of the physiological changes associated with supine compared with sitting posture in CTRL and patients with COPD is shown in **table 4**.

In COPD patients, sitting-to-supine change in  $CL_{dyn}$  correlated with corresponding changes in elastic WOB ( $r=0.74$ ,  $p=0.003$ ). In addition, sitting-to-supine change in dyspnoea

intensity correlated with corresponding changes in IND ( $r=0.65$ ,  $p=0.01$ ), NMD ( $r=0.73$ ,  $p=0.002$ ) and neuro-ventilatory uncoupling ( $r=0.76$ ,  $p=0.001$ ), **figure 3**.

## DISCUSSION

The results support the hypothesis that, compared with healthy controls, transition from sitting to supine position in mechanically compromised patients with COPD was associated with acutely increased dyspnoea intensity that was linked to corresponding increases in neuromechanical dissociation of the respiratory system due to sudden decreases in dynamic lung compliance.

This study included a well-characterized group of patients with severe airway obstruction, lung hyperinflation, persistent chronic dyspnoea and orthopnoea. Compared with healthy controls, patients had higher ventilatory requirements, IND (~2-fold), inspiratory effort and WOB together with lower IC and IRV, regardless of the position. Additionally, patients had higher resistive and elastic loading of functionally weaker inspiratory muscles compared with controls.

In healthy individuals, supine positioning was associated with a small (albeit significant) drop in  $\dot{V}_E$  at a given  $\dot{V}CO_2$  primarily due to reduced  $Fb$  (**figure 1**), without any change in respiratory sensation (31,32). Interestingly, IC increased in recumbency (by 0.48 L) in the current study (**figure 1**), consistent with an earlier report by Brody *et al.* (33). This increase in IC suggests a relatively large decrease in supine EELV, assuming TLC remained unchanged as previously reported (34,35). It is noteworthy that maximal inspiratory oesophageal and trans-diaphragmatic pressures slightly decreased in recumbency suggesting reduced functional static inspiratory muscle strength. Based on previous studies, reduction in supine EELV was likely due to a combination of decreased chest wall compliance, increased thoracic blood volume, gravitational re-distribution of visceral weight and cephaloid shift of the diaphragm (33,36-38).

Recumbency in the healthy elderly is associated with increased small airway closure, more uneven distribution of inspired gas and ultimately greater heterogeneity in mechanical time constants (i.e. product of compliance and resistance) with preferential ventilation of alveolar units with fast time constants for emptying (7,8). Indeed, in our CTRL group (average age 69 years), EFL (as crudely assessed by the VT tidal vs. maximal flow-volume loop method (30)) was increased and dynamic lung compliance was decreased in the supine position with little change in total airway resistance (6). The decrease in dynamic lung compliance in the supine position did not have a deleterious effect on respiratory symptoms in healthy controls: it led to a slight, albeit insignificant, increase in the elastic WOB which was accommodated by normally-functioning inspiratory muscles in the setting of normal respiratory mechanics.

As such, despite these acute dynamic mechanical changes and small decreases in maximal inspiratory pressures, IND for a given VT or  $\dot{V}_E$ , WOB and neuromuscular efficiency of the diaphragm were not different in supine versus seated positions in CTRL (**table 3, figure 2**). This latter finding is in keeping with previous observations that effective compensatory mechanisms are at play in health (39,40). One such adaptation is that cephaloid shift of the diaphragm is associated with improvement in length-tension relationship and increased zone of apposition which helps to preserve its ventilatory function and mitigate a fall in alveolar ventilation in the supine position (39,40).

COPD patients transitioning to the supine position reported abrupt onset of unpleasant respiratory sensations (**table 2**). In contrast to CTRL, the relatively diminished seated IC remained unchanged on recumbency suggesting an unaltered EELV (**figure 1, *online-supplement***), which is not surprising in the setting of severe resting lung hyperinflation (10,33,35,41). VT was well preserved and there was no supine decrease in  $F_b$  as seen in CTRL.

Maximal inspiratory  $P_{es}$  was similar in both positions, but  $P_{di,max}$  and expiratory  $P_{ga,max}$  decreased on recumbency, suggesting reduced contribution of the diaphragm to overall pressure generation of the respiratory pump. In other words, additional inspiratory and accessory muscles were likely recruited during the maximal inspiratory manoeuvre to TLC while supine.

Expiratory muscle activity (tidal expiratory  $P_{ga,max}$  and end-expiratory  $P_{ga}$ ) was lower in supine versus sitting positions, suggesting reduced abdominal muscle contribution to ventilation (42-44), as previously shown by Druz and Sharp (42).

The reduced fixed IC means that VT continues to be positioned close to TLC and the upper poorly-compliant portion of the relaxed respiratory system pressure-volume relation in COPD, where there is increased elastic/threshold loading of functionally weakened inspiratory muscles. This is further compounded in recumbency by acutely decreased dynamic lung compliance by 48 ml/cmH<sub>2</sub>O in the setting of a stable breathing pattern and lack of a significant increase in airway resistance. The cause of reduced dynamic lung compliance is multifactorial and potentially include those factors mentioned above: increased small airway closure with variable atelectasis and regional lung hyperinflation, increased EFL as suggested by VT/maximal flow-volume loop overlap calculations; maldistribution of inspired gas and greater mechanical time constant inhomogeneity (45). Other possible contributors established from previous studies include gravitational effects such as increased pulmonary blood volume and increased thoraco-abdominal asynchrony and chest wall distortion leading to reduced lung distensibility (7,45).

Unlike the situation in CTRL, acute elastic loading of this nature had immediate deleterious consequences in these individuals who were already mechanically compromised (by resting hyperinflation and impaired inspiratory muscle function). Effort and WOB of the inspiratory muscles increased in association with an augmented IND. While neuromuscular efficiency of the diaphragm was largely unaltered, overall compensatory strategies were less

effective than in CTRL. Thus, the wide disparities between increased IND and the mechanical and ventilatory responses of the respiratory system evident while sitting were acutely amplified by adopting the supine posture.

On recumbency and despite the compensatory increase in IND in patients with COPD, there was a modest reduction in  $\dot{V}_E$  but the ventilatory equivalent for  $\dot{V}CO_2$ , which would be expected to rise due to decreased ventilatory efficiency, actually fell significantly by 5 L/min in keeping with acute mechanical deterioration and associated ventilatory constraints. This was associated with a small rise in  $P_{et}CO_2$  and reduction in  $SpO_2$  of uncertain clinical significance.

### ***Mechanisms of orthopnoea in patients with COPD***

Dyspnoea intensity (severity) was increased in the supine versus sitting posture by an average of 1.2 Borg units in our patients (**table 2**). In qualitative terms, patients described greater difficulty in breathing in and out, and reported “my breathing requires more work or effort” and “my breathing feels unpleasant”. In general, greater dyspnoea is associated with greater IND and inspiratory effort as a result of greater mechanical loading of the inspiratory muscles, increased chemical drive or both in combination (16). The sudden increase in acute elastic mechanical loading worsened load/capacity imbalance of the inspiratory muscles, such that compensatory increases in IND were required. Accordingly, the data support the postulation that increased central command output from cortical motor centers to the inspiratory muscles and the attendant increased central corollary discharge from these centers to the somato-sensory cortex are key mechanisms of orthopnoea (46). However, altered afferent inputs from abundant sensory receptors throughout the respiratory system (which cannot be easily measured), in response to sudden increases in elastic loading, also likely influenced perception of the intensity and quality of dyspnoea. Certainly, it is reasonable to implicate short term alterations in afferent feedback from mechanoreceptors in the inspiratory muscles and the chest wall (muscle spindles and Golgi



tendon organs) in the genesis of such unpleasant respiratory sensations (47). In the current study, the consistent association between increases in respiratory discomfort in the sitting-supine transition and parallel increases in measures of IND, NMD and neuro-ventilatory mismatching (explaining 40-50% of the variance in orthopnoea) further support this contention (**figure 3**).

### **Limitations**

The sample size is small, but was sufficient to uncover significant differences in the parameters of interest between patients and CTRL and within patients (15,16). We obtained EMG measurements of the crural diaphragm only and cannot comment on concomitant electrical activity of the ribcage and accessory muscles. We must acknowledge, when considering positional differences in the mechanical properties of the lungs, that intra-oesophageal pressure can deviate from intra-pleural pressure in the supine position due to a direct pressure of the heart or other mediastinal structures on the oesophagus (6). Our study did not permit us to assess potential “peripheral” influences on the intensity/quality of perceived orthopnoea, that may arise directly from altered afferent feedback from various sensory receptors in the respiratory muscles, chest wall, lungs and cardio-vascular system. Lastly, we acknowledge that our results cannot be generalized to all COPD patients; those without orthopnoea or those with significant comorbidities.

### **Conclusion**

In patients with severe COPD, onset of orthopnoea coincided with an abrupt increase in amplitude of IND from an already elevated sitting value. This increased IND occurred in response to acute elastic loading of the functionally weakened inspiratory muscles and further amplified the pre-existing disparity between increased IND and the mechanical and ventilatory responses of the respiratory system.

Our study is the first to demonstrate that the presence of persistent orthopnoea in patients with advanced COPD points to the existence of severe mechanical compromise and very high resting IND and NMD, even in the absence of significant pulmonary gas exchange abnormalities. The corollary is that a central goal of management in such patients must be to improve respiratory mechanics so as to effectively reduce IND and NMD, as recently demonstrated (48). To the extent that orthopnoea can seriously disrupt sleep in patients with advanced COPD, every effort should be made to individualize bronchodilator treatment to achieve sustained “24-hour” bronchodilatation and lung deflation.

**Author Contribution:** All the authors played a role in the content and writing of the manuscript. In addition, D.E.O. was the principal investigator and provided the original idea for the study; D.E.O and A.F.E. had input into the study design and conduct of the study. A.F.E. and H.M. collected the data; A.F.E. and A.F. performed data analysis and prepared it for presentation.

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**Table 1: Subjects Characteristics and Pulmonary Function Test**

Variable	COPD (n=16, M:F= 9:7)	CTRL (n=16, M:F= 8:8)
Age, years	66±7	69±7
Height, cm	168±10	167±7
Body mass, Kg	71±17	76±11
BMI, Kg/m <sup>2</sup>	25±6	27±3
Smoking history, pack-years	52.2±24.9*	1.8±3.5
Smoking status, % current smokers	25	0
Modified MRC dyspnoea scale (0-4)	2.7±0.9*	0.2±0.4
BDI focal score (0-12)	5.0±1.8*	11.6±0.7
Pulmonary Function Test		
FEV <sub>1</sub> , L	0.96±0.39* (40±18*)	2.70±0.63 (115±28)
FVC, L	2.67±0.86* (73±15*)	3.74±0.66 (110±15)
FEV <sub>1</sub> /FVC, %	37±14* (53±20*)	70±7 (101±11)
PEF, L/s	3.54±1.28* (53±22*)	7.40±1.32 (113±15)
FEF <sub>25-75%</sub> , L/s	0.35±0.18* (14±8*)	1.82±0.96 (75±38)
IC, L	1.89±0.55* (69±16*)	2.99±0.74 (114±20)
FRC, L	4.92±1.77* (151±42*)	3.15±0.63 (100±16)
TLC, L	6.81±1.91 (113±18)	6.05±0.93 (105±10)
RV, L	3.80±1.43* (172±60*)	2.11±0.54 (94±18)
RV/TLC, %	55±11*	35±7
D <sub>L</sub> CO, ml/min/mmHg	7.67±2.85* (40±18*)	17.72±3.61 (89±17)
D <sub>I</sub> /V <sub>A</sub> , ml/min/mmHg/L	2.06±0.69* (52±24*)	3.38±0.53 (92±13)
V <sub>A</sub> , L	3.85±0.87*	5.25±0.80
V <sub>A</sub> /TLC	0.53±0.19*	0.87±0.06
sRaw, cmH <sub>2</sub> O•s	28.9±16.4* (686±385*)	7.7±4.6 (184±104)
MVV, L/min	35.8±11.0* (32±13*)	109.6±27.3 (107±20)
MIP, cmH <sub>2</sub> O	66±21* (80±39*)	100±32 (134±39)
MEP, cmH <sub>2</sub> O	114±40 (57±30*)	133±61 (79±27)

Values are means±SD. Percentage of predicted normal values for pulmonary function test are shown in parentheses. \* p<0.05 COPD vs. CTRL group.

*Abbreviations:* BDI= Baseline Dyspnoea Index; BMI= body mass index; COPD= chronic obstructive pulmonary disease; CTRL= healthy controls; D<sub>L</sub>CO = diffusing capacity of the lung for carbon monoxide; D<sub>I</sub>/V<sub>A</sub> = D<sub>L</sub>CO corrected for alveolar volume; F= female; FEF<sub>25-75%</sub>= forced expiratory flow between 25 and 75% of forced vital capacity; FEV<sub>1</sub>/FVC= ratio between FEV<sub>1</sub> and forced vital capacity; FEV<sub>1</sub>= forced expired volume in 1 s; FRC= functional residual capacity; FVC= forced vital capacity; IC= inspiratory capacity; M= male; MEP= maximum expiratory mouth pressure; MIP= maximum inspiratory mouth pressure; MRC= Medical Research Council; MVV= maximal voluntary ventilation; PEF= peak expiratory flow; RV= residual volume; sRaw= specific airway resistance; TLC= total lung capacity, V<sub>A</sub>= alveolar volume.

**Table 2: Cardio-respiratory and metabolic measurements in sitting and supine positions**

Variable	COPD (n=16)		CTRL (n=16)	
	Sitting	Supine	Sitting	Supine
$\dot{V}O_2$ , L/min	0.26±0.05	0.26±0.06	0.28±0.06	0.29±0.05
$\dot{V}CO_2$ , L/min	0.21±0.05	0.21±0.05	0.23±0.05	0.21±0.04
$\dot{V}_E$ , L/min	12.11±1.7†	11.20±1.76†	9.75±1.97*	8.46±1.87
IC, L	2.05±0.73†	2.13±0.78†	3.02±0.79*	3.49±0.77
VT, L	0.65±0.16	0.62±0.19	0.68±0.14	0.67±0.12
Fb, breaths/min	19.9±4.4†	19.7±6.1†	15.3±3.0*	13.4±3.3
$T_I/T_{TOT}$	35.3±5.8†	37.1±7.2†	44.8±5.3*	55.1±9.5
$T_I$ , sec	1.19±0.26†	1.58±1.17†	2.03±0.70*	3.06±1.22
IRV, L	1.35±0.57*†	1.46±0.61†	2.33±0.72	2.70±1.13
$\dot{V}_E/\dot{V}O_2$	47.7±6.1*†	42.5±5.8†	35.9±6.0*	29.3±3.5
$\dot{V}_E/\dot{V}CO_2$	59.1±9.6*†	54.3±8.1†	44.6±6.2*	40.1±4.5
PetCO <sub>2</sub> , mmHg	31.8±4.7*	33.0±4.2	34.2±3.2	34.6±1.9
Heart rate, beats/min	72±8	70±9	70±10*	65±7
SpO <sub>2</sub> , %	94.5±2.4*	93.8±2.6	95.4±1.4*	94.2±1.1
V <sub>FL</sub> , %	83.7±12.0*†	95.6±5.9†	25.5±29.6*	67.0±27.0
Dyspnoea (Borg scale 0-10)				
▪ Overall intensity	0.78±0.89*†	2.00±1.20†	0.0±0.0	0.0±0.0
▪ Difficulty breathing in	0.50±0.82*†	1.38±1.30†	0.0±0.0	0.0±0.0
▪ Difficulty breathing out	0.56±0.85*†	1.25±1.24†	0.0±0.0	0.0±0.0
▪ Work / effort	0.44±0.77*†	1.72±1.53†	0.0±0.0	0.0±0.0
▪ Unpleasantness	0.53±0.85*†	1.69±1.48†	0.03±0.13	0.10±0.21

Values are means±SD.

\*p<0.05 sitting vs. supine within COPD or CTRL. †p<0.05 COPD vs. CTRL.

*Abbreviations:*  $\dot{V}CO_2$ = carbon dioxide production;  $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for carbon dioxide;  $\dot{V}_E/\dot{V}O_2$ = ventilatory equivalent for oxygen;  $\dot{V}_E$ = minute ventilation;  $\dot{V}O_2$ = oxygen consumption; COPD= chronic obstructive pulmonary disease; CTRL= healthy controls; Fb= breathing frequency; IC= inspiratory capacity; IRV= inspiratory reserve volume; PetCO<sub>2</sub>= partial pressure of end-tidal carbon dioxide; SpO<sub>2</sub>= oxygen saturation measured by pulse oximetry;  $T_I/T_{TOT}$ = inspiratory duty cycle;  $T_I$ = inspiratory time; V<sub>FL</sub>= % of tidal volume that overlapped maximal flow volume loop; VT= tidal volume.

**Table 3: Respiratory pressures and EMGdi measurements in sitting and supine positions**

Variable	COPD (n=15)		CTRL (n=15)	
	Sitting	Supine	Sitting	Supine
<b>Inspiratory muscle activity</b>				
Inspiratory Pes, max, cmH <sub>2</sub> O	44.9±11.0†	43.0±13.6†	67.4±17.0*	61.2±17.6
Tidal inspiratory Pes, cmH <sub>2</sub> O	9.9±2.8†	10.5±3.8†	3.2±1.7	4.2±2.4
Tidal Pes <sub>%max</sub> , %	24±11*†	29±17†	5±3*	7±5
Pdi, max, cmH <sub>2</sub> O	79±23*†	69±20†	96±18*	80±21
Tidal Pdi, cmH <sub>2</sub> O	10.4±2.6†	11.6±3.2†	5.4±2.6	5.8±3.8
Tidal Pdi <sub>%max</sub> , %	14±5*†	19±10†	6±3	8±6
Tidal Pdi <sub>%max</sub> :VT <sub>%predVC</sub>	0.75±0.31*†	1.10±0.65†	0.30±0.17	0.40±0.29
<b>Expiratory muscle activity</b>				
Tidal expiratory Pga, max, cmH <sub>2</sub> O	24.6±13.4*	18.1±12.9	17.7±9.7*	12.6±7.3
Pga, end expiratory, cmH <sub>2</sub> O	22.3±14.2*	17.0±13.5	15.0±10.8*	11.2±7.9
<b>EMGdi measurements</b>				
Tidal EMGdi, µV	46.9±17.4†	50.4±19.6†	20.1±8.0	17.4±6.8
EMGdi,max, µV	185±42*	160±58	164±33*	139±26
EMGdi <sub>%max</sub> : $\dot{V}_E$	2.10±0.69*†	2.93±1.17†	1.37±0.64	1.57±0.74
EMGdi <sub>%max</sub> , %	25±7*†	33±13†	13±6	13±5
EMGdi <sub>%max</sub> :VT <sub>%predVC</sub>	1.35±0.49*†	1.92±1.10†	0.66±0.37	0.65±0.28
EMGdi <sub>%max</sub> :tidal Pdi <sub>%max</sub>	2.06±1.08	2.21±1.29	2.74±1.41	3.05±2.87
<b>Extra measurements of respiratory mechanics</b>				
CL,dyn, ml/cmH <sub>2</sub> O	168±96*†	120±77†	281±83*	232±106
Airway resistance, cmH <sub>2</sub> O/L/sec	7.40±3.09†	7.74±3.45†	1.80±1.14	2.42±1.60
Total inspiratory WOB (J)	7.17±2.37*†	10.16±4.14†	1.87±1.28	2.46±1.86
Total expiratory WOB (J)	1.76±0.81†	1.36±1.20†	0.16±0.21	0.17±0.24
Elastic WOB (J)	3.10±0.98†	4.21±2.39†	1.16±0.75	1.64±1.20
Resistive WOB (J)	4.07±1.60†	4.95±2.35†	0.71±0.66	0.82±0.71

Values are means±SD. \*p<0.05 sitting vs. supine within COPD or CTRL. †p<0.05 COPD vs. CTRL.

*Abbreviations:* CL,dyn =dynamic lung compliance; COPD= chronic obstructive pulmonary disease; CTRL= healthy controls; EMGdi<sub>%max</sub>: $\dot{V}_E$ =neuro-ventilatory coupling; EMGdi<sub>%max</sub>:tidal Pdi<sub>%max</sub>= neuromuscular efficiency of the diaphragm; EMGdi<sub>%max</sub>:VT<sub>%predVC</sub>= measure of neuromechanical dissociation of the respiratory system; EMGdi<sub>%max</sub>= measure of inspiratory neural drive to the diaphragm; EMGdi= diaphragm electromyography; Pdi= trans-diaphragmatic pressure; Pes= oesophageal pressure; Pga= gastric pressure; tidal expiratory Pga,max = the maximum expiratory gastric pressure during tidal breathing; VC= vital capacity; V<sub>T</sub>= tidal volume;  $\dot{V}_E$ = minute ventilation; WOB= work of breathing.



**Table 4: Summary of physiological changes associated with supine posture compared with sitting posture**

Variable	Patients with advanced COPD and orthopnoea	Healthy controls
Inspiratory capacity, L	-	↑
EELV, L	-	↓
Minute ventilation, L/min	-	↓
$\dot{V}_E/\dot{V}CO_2$	↓	↓
Tidal volume, L	-	-
Dynamic compliance, ml/cmH <sub>2</sub> O	↓	↓
Inspiratory effort (Tidal Pdi <sub>%max</sub> )	↑	-
Expiratory muscle activity	↓	↓
Total inspiratory WOB, J	↑	-
Inspiratory neural drive (Tidal EMGdi <sub>%max</sub> )	↑	-
Neuromechanical dissociation	↑	-
Neuroventilatory uncoupling	↑	-
Dyspnoea Borg ratings	↑	-

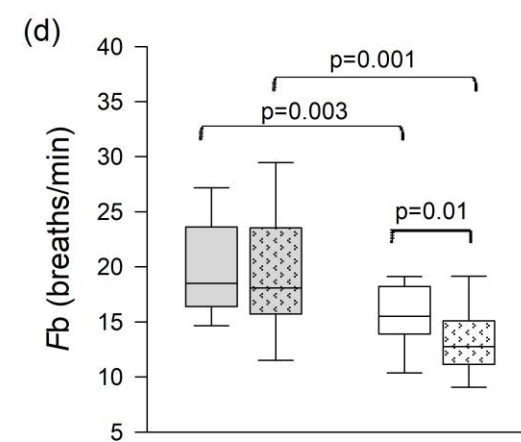
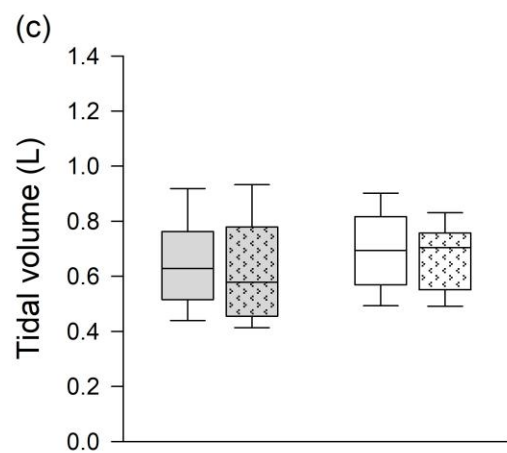
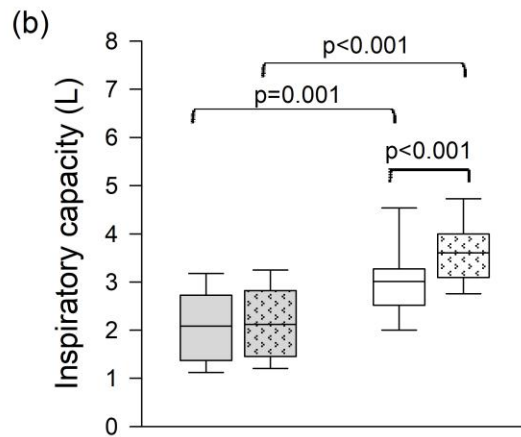
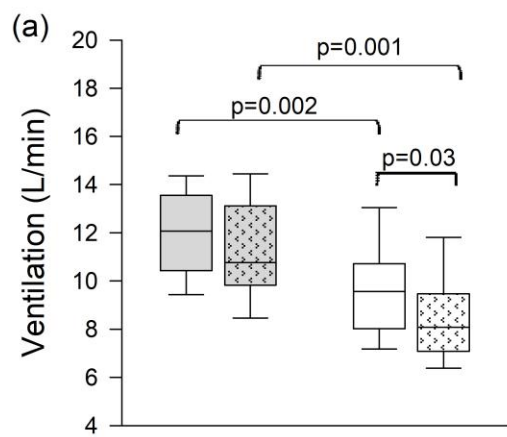
*Abbreviations:*  $\dot{V}_E/\dot{V}CO_2$ = ventilatory equivalent for carbon dioxide; COPD= chronic obstructive pulmonary disease; EELV= end-expiratory lung volume; EMGdi= diaphragm electromyography; Pdi= trans-diaphragmatic pressure; WOB= work of breathing.

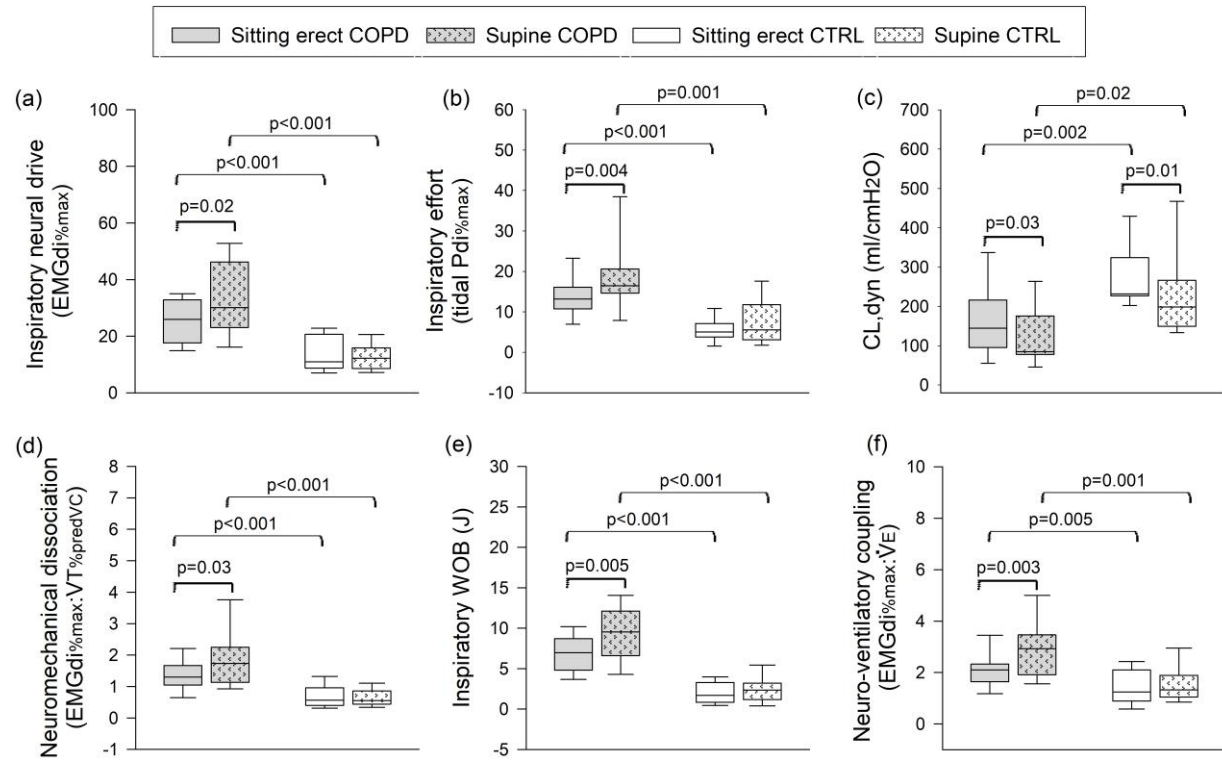
## Figure Legends

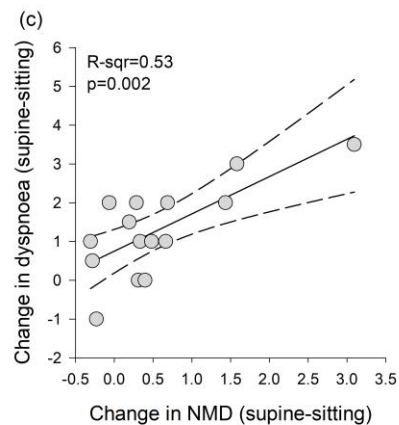
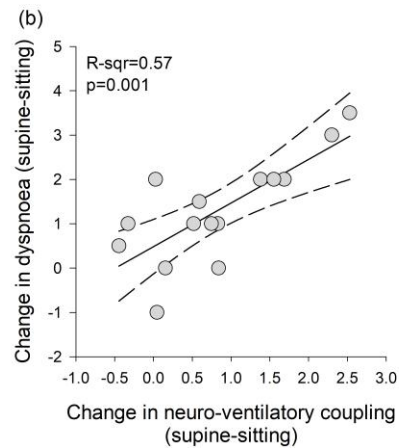
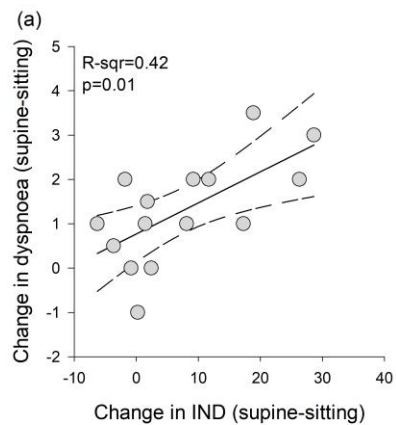
**Figure 1.** Breathing pattern parameters in sitting and supine positions in patients with advanced COPD and age-matched healthy controls (CTRL). Boxes depict the first to third quartiles; central lines denote the median. Whiskers range from the 10th to the 90th percentile. *Abbreviations:* COPD= chronic obstructive pulmonary disease; *Fb*= breathing frequency.

**Figure 2.** Inspiratory neural drive by diaphragm electromyography (EMGdi) and respiratory pressure measurements in sitting and supine positions in patients with advanced COPD and age-matched healthy controls (CTRL). Boxes depict the first to third quartiles; central lines denote the median. Whiskers range from the 10th to the 90th percentile. *Abbreviations:* COPD= chronic obstructive pulmonary disease; CL<sub>dyn</sub>= dynamic lung compliance; Pdi= trans-diaphragmatic pressure; WOB= work of breathing;  $\dot{V}_E$ =minute ventilation;  $V_T$ = tidal volume.

**Figure 3.** There was a significant correlation between supine-sitting change in dyspnoea intensity (Borg scale) and corresponding changes in: (a) inspiratory neural drive (IND) (r-square=0.42, p=0.01); and (b) neuro-ventilatory coupling (r-square=0.57, p=0.001) and (c) neuromechanical dissociation (NMD) (r-square=0.53, p=0.002). Dashed lines represent the 95% confidence intervals for the slope of the regression line.







# **Mechanisms of Orthopnoea in Patients with Advanced COPD**

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## **ONLINE DATA SUPPLEMENT**

### **Methods**

#### **Pulmonary function test**

Spirometry, body plethysmography, single-breath lung diffusing capacity for carbon monoxide ( $D_LCO$ ) and maximal inspiratory (MIP) and expiratory (MEP) mouth pressures were performed using automated equipment (Vmax229d, AutoboxV62J; SensorMedics, Yorba Linda, CA). Measurements were expressed relative to predicted normal values (1,2).

#### **Diaphragm electromyography and respiratory pressure measurements**

Diaphragm electromyography (EMGdi), oesophageal pressure (Pes) and gastric pressure (Pga) were measured continuously using a combined electrode-balloon catheter system (3-7). The EMGdi signal was sampled at 2000 Hz (PowerLab, model ML880; ADInstruments, Castle Hill, NSW, Australia), band-pass filtered between 20-1000 Hz (Bioamplifier model RA-8; Guanzhou Yinghui Medical Equipment Co. Ltd, Guangzhou, China) and converted to a root mean square (RMS) to assess respiratory neural activity. The data from the electrode pair showing the highest RMS value from the five electrode pairs in each inspiration was used for analysis. The oesophageal and gastric balloons were inflated with 1.0 mL and 1.2 mL of air, respectively. Pes and Pga were measured using differential pressure transducers (model DP15-34; Validyne Engineering, Northridge, CA, USA) and sampled at a rate of 100 Hz (PowerLab); trans-diaphragmatic pressure (Pdi) was calculated by subtraction of Pes from Pga. The continuous flow signal from the Vmax229d system (SensorMedics, Yorba Linda, CA) was simultaneously input into the data-acquisition system for analysis.

Maximal EMGdi (EMGdi,max) was determined as the highest inspiratory RMS from any sniff/inspiratory capacity manoeuvre performed during the test (8). Inspiratory sniffs were used to obtain maximum Pes (Pes,max) and maximum Pdi (Pdi,max) (6,9). Tidal Pes swings (Pes, tidal) were defined as the amplitude between the maximum expiratory value and minimum inspiratory value for each respiratory cycle. The tidal Pdi swing was defined as the amplitude of the Pdi waveform during tidal breathing.

End-inspiratory (EI) and end-expiratory (EE) data points of zero flow for Pes and Pga were collected. Dynamic compliance (CL,dyn) was calculated as the change in lung volume divided by change in Pes between EE and EI (10). Lung elastic work was calculated from the dynamic relation between Pes and lung volume in Campbell diagrams (11,12). Airway resistance was calculated as the difference in Pes divided by the difference in flow at inspiratory mid-volume and expiratory iso-volume ( $\Delta\text{Pes}/\Delta\text{flow}$ ) (10).

EMGdi<sub>%max</sub> was used as an index of inspiratory neural drive (IND) to the crural diaphragm. The ratio between EMGdi<sub>%max</sub> and tidal volume expressed relative to predicted vital capacity (EMGdi<sub>%max</sub>:VT<sub>%predVC</sub>) was used as an index of neuromechanical dissociation (NMD) of the respiratory system (9). Neuromuscular efficiency of the diaphragm was defined as the ratio of EMGdi<sub>%max</sub>:tidal Pdi<sub>%max</sub> (6).

## Results

Compared with healthy controls, patients with COPD had greater COPD assessment test (CAT) score, poorer health-related quality of life (St. George's Respiratory Questionnaire) and lower habitual physical activity (Community Healthy Activities Model Program for Seniors questionnaire), all  $p < 0.001$  (**table E1**). In average, patients had severe airflow obstruction [forced expiratory volume in one-second (FEV<sub>1</sub>):  $40 \pm 18$  %predicted] and 4/16 had moderate severity ( $80 > \text{FEV}_1 \geq 50$  %predicted). **Table E1** also shows subjects' comorbid conditions and medications.

None of the subjects had significant cardiovascular or pulmonary vascular disease that could contribute to dyspnoea or orthopnoea.

In supine (vs. sitting), controls' inspiratory capacity (IC) increased by 0.48L ( $p<0.001$ ) (**figure E1**) likely reflecting lower end-expiratory lung volume (EELV). In contrast to controls, patients' IC and EELV were similar in both positions (**figure E1**).

Patients had greater dyspnoea in all 5 domains in both positions compared with healthy controls (all  $p<0.05$ ) and dyspnoea ratings increased significantly in the transition from seated to supine position in patients ( $p<0.05$ ), **figure E2**.

Fifteen of sixteen participants in each group accepted the insertion of the EMGdi-pressure catheter. EMGdi,max and Pdi,max were lower in supine versus sitting positions in both groups ( $p<0.05$ ) (**figure E3 and E4**). While tidal EMGdi and Pdi were not significantly different between positions, values were greater in COPD patients compared with controls regardless of the position.

EMGdi<sub>%max</sub> and tidal Pdi<sub>%max</sub> were greater in supine versus sitting position only in patients with COPD and values remained unaltered in healthy controls. Looking at individual EMGdi data (**figure E3**), 53% of patients showed a rise in tidal EMGdi in supine versus sitting position and the mean value tended to be higher while supine, though not significant. As such, higher EMGdi<sub>%max</sub> in supine versus sitting position in patients with COPD was a result of both higher numerator and lower denominator in variable combination. While in healthy controls, the majority (73%) showed a drop in their tidal EMGdi in supine versus sitting (**figure E3**). Similarly, higher tidal Pdi<sub>%max</sub> in supine versus sitting position in COPD patients was a result of higher tidal Pdi (i.e. numerator) and lower Pdi,max (i.e. denominator) in variable combination (**figure E4**).



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**Table E1: Subjects Characteristics**

Variable	COPD (n=16)	CTRL (n=16)
CAT score (0-40)	21.3±7.8*	4.3±3.5
SGRQ total score	50.7±14.3*	3.4±1.8
CHAMPS, kcal/wk for all activities	2102±1843*	5342±4240
Comorbidities, no of subjects (%)		
▪ Hypertension	7 (44)	6 (38)
▪ Diabetes Mellitus	2 (13)	2 (13)
▪ Ischaemic heart disease	3 (19)	0 (0)
▪ Hypercholesterolemia	6 (38)	5 (31)
▪ Anxiety	2 (13)	2 (13)
▪ Depression	3 (19)	2 (13)
▪ Osteoporosis	3 (19)	0 (0)
Inhaled medication usage, no of subjects (%)		
▪ SABA	15 (94)	0 (0)
▪ SAMA	7 (44)	0 (0)
▪ LAMA	5 (31)	0 (0)
▪ Combined LABA/LAMA	8 (50)	0 (0)
▪ ICS	7 (44)	0 (0)
▪ Combined ICS/LABA	5 (31)	0 (0)
Other medications, no. of subjects (%)		
▪ Anti-hypertensive	7 (44)	6 (38)
▪ Statin	6 (38)	5 (31)
▪ Anti-depressant	3 (19)	2 (13)
▪ Thyroid replacement	1 (6)	1 (6)
▪ Anti-angina medication	2 (13)	0 (0)
▪ Aspirin	2 (13)	1 (6)

Values are means±SD.

\* p<0.05 COPD vs. CTRL group.

*Abbreviations:* CAT= COPD Assessment Test; CHAMPS= Community Healthy Activities Model Program for Seniors questionnaire; COPD= chronic obstructive pulmonary disease; CTRL= healthy controls; ICS= inhaled corticosteroid; LABA= long-acting beta<sub>2</sub>-agonist; LAMA= long-acting muscarinic antagonist; SABA= short-acting beta<sub>2</sub>-agonist; SAMA= short-acting muscarinic antagonist; SGRQ= St. George's Respiratory Questionnaire.

## Figure Legends

**Figure E1.** Resting lung volumes in sitting and supine positions in patients with advanced COPD and age-matched healthy controls. Note the significant increase in inspiratory capacity (IC) in healthy controls while supine by 0.48 L ( $p<0.001$ ) as a result of reduced EELV; assuming total lung capacity did not change with posture. The small sitting IC remained unaltered while supine in patients with COPD. *Abbreviations:* COPD= chronic obstructive pulmonary disease; EELV= end-expiratory lung volume; IRV= inspiratory reserve volume;  $V_T$ = tidal volume.

**Figure E2:** Qualitative dyspnoea descriptors using the modified 10-point Borg scale in sitting and supine positions in patients with advanced COPD. Boxes depict the first to third quartiles; central lines denote the median. Whiskers range from the 10th to the 90th percentile.  $*p<0.05$  sitting versus supine in patients with COPD.

**Figure E3.** Individual diaphragm electromyography (EMGdi) data are shown in patients with advanced COPD and age-matched healthy controls (CTRL). Data are shown as absolute tidal inspiratory EMGdi (panels (a) and (b)) and as maximum values during serial sniff or inspiratory capacity manoeuvres (EMGdi,max) (panels (c) and (d)) in supine and sitting positions. Square symbols represent means.  $*p<0.05$  sitting versus supine in patients or CTRL. *Abbreviations:* COPD= chronic obstructive pulmonary disease, CTRL= healthy controls.

**Figure E4.** Individual trans-diaphragmatic pressure (Pdi) data are shown in patients with advanced COPD and age-matched healthy controls (CTRL). Data are shown as absolute tidal Pdi (panels (a) and (b)) and as maximum values during serial sniff manoeuvres (Pdi,max) (panels (c) and (d)) in supine and sitting positions. Square symbols represent means.  $*p<0.05$  sitting versus supine in patients or CTRL. *Abbreviations:* COPD= chronic obstructive pulmonary disease, CTRL= healthy controls.

